

Responses to Major Comments on Technical Support Document

Public Health Goal For Carbofuran In Drinking Water

Prepared by

**Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency**

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INTRODUCTION

The following are responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for carbofuran as discussed at the PHG workshop held on November 5, 1999, or as revised following the workshop. Some commenters provided comments on both the first and second drafts. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they are directly quoted from the submission; paraphrased comments are in italics.

These comments and responses are provided in the spirit of the open dialogue among scientists that is part of the process under Health and Safety Code Section 57003. For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA Web site at www.oehha.org. OEHHA may also be contacted at:

Office of Environmental Health Hazard Assessment
301 Capitol Mall, Room 205
Sacramento, California 95814
(916) 324-7572

RESPONSES TO MAJOR COMMENTS RECEIVED

United States Environmental Protection Agency Office of Drinking Water

Comment: *Recommend not finalizing PHG until the United States Environmental Protection Agency (U.S. EPA) completes its own RfD reassessment, which was identified as “likely...before the end of December, 1999.”*

Response: Considering the long delays in U.S. EPA assessments and the strict timetable for PHG preparation specified in California statutes, we usually proceed with our own analyses. We decided to do so in this case. The revised RfD is still not posted on U.S. EPA’s IRIS site as of July, 2000.

University of California, Berkeley

Comment 1: *Prefer that cholinesterase information be compared directly with testicular and sperm changes.*

Response 1: In the Pant et al. study, cholinesterase activity was not measured, so a direct correlation between inhibition and testicular effects is not possible. We have attempted to place these testicular changes in the context of doses causing cholinesterase inhibition in several places in the document, including Table 3 and the ensuing discussion.

Comment 2: *Recommend including a reference to Stehrer-Schmid and Wolf (1995) as supporting the reproductive effects reported by Pant et al. (1995). Stehrer-Schmid and Wolf (1995) reported effects of carbofuran on microtubules, and sperm are full of microtubules.*

Response 2: In the Stehrer-Schmid and Wolf (1995) study, high concentrations of carbofuran (and three other carbamates) were incubated with a preparation of brain tubulin. Carbofuran appeared to increase the rate of assembly of tubulin at 0.5 mmol/L, and decreased it at 1 mmol/L and higher. These very high concentrations are not achievable in vivo; death from cholinesterase inhibition occurs at doses that produce tissue concentrations lower by several orders of magnitude. Brain changes that might reflect effects on tubulin assembly are also not noted in chronic studies. Therefore these in vitro observations did not appear relevant to nor supportive of an interpretation of the testicular effects, and the study has not been cited.

Comment 3: “A major omission is reference to the published information on the human toxic effects of carbofuran.” *A list of four references was included.*

Response 3: The indicated studies are now cited, except for the Gupta (1994) article, which is a review of several aspects of carbofuran toxicity, emphasizing Dr. Gupta’s work. The PHG addresses Dr. Gupta’s work from his original sources. Another of the studies (identified from a note in Journal of the American Medical Association) is now cited in the PHG from the original article in the Morbidity and Mortality Weekly Report.

Comment 4: *Miscellaneous editorial comments.*

Response 4: Good comments, most of which have been incorporated into the document. However, epididymides was spelled correctly.

University of Southern California School of Medicine

Comment 1: *The major comment was that the toxicity of carbofuran appeared to be about the same in dog, rat, and human, and that choice of a rat study for the PHG introduced an unnecessary extra 10-fold uncertainty factor for intraspecies extrapolation. He recommended a 30-fold UF for the human study.*

Response 1: The human study is not an adequate basis for the PHG, in our opinion, because it employed acute administration and small group sizes. A particular limitation is that the testicular toxicity observed in the animal study would not be detectable in the acute human study. If the human study were used, we would incorporate an uncertainty factor of 100 (10 for acute to chronic extrapolation and 10 for human variability). The resulting value would be 7 ppb instead of the 1.7 ppb value chosen. The similarity in risk assessment values appears to reinforce the reviewer's main point, but we believe that extrapolation from the subchronic rat study of Pant et al. provides a more appropriate basis for the PHG.

Comment 2: "Throughout this PHG document on carbofuran, the authors did not emphasize whether the toxicity at many of the endpoints studied was dose-dependent."

Response to Comment 2: Dose-dependency is a major review criterion that therefore tends to be taken for granted; we are more likely to note when an effect is not dose-dependent. After reviewing the information presented in the sections addressing toxicity, we feel that the dose-response descriptions are adequate for the intended purposes.

Comment 3: *The reviewer indicated that the manner of calculating the adjusted daily dose for the PHG calculation was not clear.*

Response 3: A correction and edits were made to the text, which should clarify this point.

Comment 4: *The reviewer suggested a more conservative interpretation of the genotoxicity data. Carbofuran could still be a potential carcinogen; NTP still needs to conduct a definitive study. Suggest OEHHHA include a narrative to discuss the studies, and point out the fact that important mammalian toxicity assays (mutation to 6-thioguanine or ouabain resistance, for instance) were not conducted.*

Response 4: OEHHHA has modified its interpretation of the genotoxicity data on carbofuran to identify it as a possible weak mutagen. However, there is little basis for considering carbofuran as a potential carcinogen. Three adequate chronic studies in three species have indicated no dose-dependent increases in tumors. With the rather weak mutagenic potential, there is no incentive for NTP to conduct another chronic study. A narrative to summarize and evaluate the genotoxicity data in Table 2 has been included. Carbofuran has met the genotoxicity testing requirements under FIFRA, and contains the representative assays for all types of known genotoxic mechanisms; a more extensive battery of mammalian somatic cell assays is not required and does not appear to us to be necessary. OEHHHA had located a V79 test for

ouabain resistance that was not included in the table because of concerns over the study adequacy, i.e. nonstandard test and inadequate characterization of the test substance. This study's data has been included in Table 2.

Comment 5: *Add some discussion of which metabolites are toxic or carcinogenic.*

Response 5: Unfortunately, there is limited information on the toxicity of carbofuran metabolites. All that is known is their potency for cholinesterase inhibition compared to carbofuran. This was mentioned in the text.

Comment 6: "It would be clearer if NOAEL/LOAEL [in the example PHG calculation] were replaced with (NOAEL or LOAEL)."

Response 6: Right below the equation, the definition of terms states that this factor means NOAEL or LOAEL, so this shouldn't be a matter of much confusion. Because this is a part of our standard format, we decided not to change it just for this document.

Comment 7: "Please describe concisely why the next PHG should be 10-20 times lower than the State MCL and the Federal MCL."

Response 7: The explanation has been added to the Summary as requested, noting that the PHG is based on a study not available to the previous reviewers.

Comment 8: *Other minor editorial suggestions were made.*

Response 8: Most of the suggestions were incorporated into the text.